cause death in at least 80 percent of injected mice.

(iv) *Standard antitoxin.* The Epsilon Antitoxin preparation which has been standardized as to antitoxin unitage on the basis of the International *Clostridium perfringens* Epsilon Antitoxin Standard and which is either supplied by or acceptable to Animal and Plant Health Inspection Service. The antitoxin unit value shall be stated on the label.

(v) *Standard toxin.* The Epsilon toxin preparation which is supplied by or is acceptable to Animal and Plant Health Inspection Service.

(vi) *Diluent.* The solution used to make proper dilutions prescribed in this test. Such solution shall be made by dissolving 1 gram of peptone and 0.25 gram of sodium chloride in each 100 ml of distilled water; adjusting the pH to 7.2; autoclaving at 250 °F. for 25 minutes; and storing at 4 °C. until used.

(2) The antitoxin content of the test sample shall be determined as follows:

(i) Make a dilution of Standard Antitoxin to contain 1 International Unit of antitoxin per ml.

(ii) Make one dilution of Standard Toxin to contain 10 L_0 doses per ml and make a second dilution of Standard Toxin to contain 10 L_+ doses per ml.

(iii) Dilute 1 ml of the test sample with 33 ml of diluent and combine 1 ml of this dilution with 1 ml of the Standard Toxin diluted to contain 10 L_0 doses.

(iv) Combine 1 International Unit of Standard Antitoxin with 10 L_0 doses of Standard Toxin and combine 1 International Unit of Standard Antitoxin with 10 L_+ doses of Standard Toxin.

(v) Neutralize all toxin-antitoxin mixtures at room temperature for 1 hour, and hold in ice water until injections of mice can be made.

(vi) Five Swiss white mice, each weighing 16–20 grams, shall be used for each toxin-antitoxin mixture. A dose of 0.2 ml shall be injected intravenously into each mouse. Conclude the test 24 hours post-injection and record all deaths.

(3) Test Interpretation. (i) If any mice inoculated with the mixture of 1 International Unit of Standard Antitoxin and 10 L_0 doses of Standard Toxin die, the results of the test are inconclusive and shall be repeated: *Provided,* That, if the test is not repeated, the serial shall be declared unsatisfactory.

(ii) If less than 80 percent of the mice inoculated with mixture of 1 International Unit of Standard Antitoxin and 10 L_+ doses of Standard Toxin die, the results of the test are inconclusive and shall be repeated: *Provided,* That, if the test is not repeated, the serial shall be declared unsatisfactory.

(iii) If any mice inoculated with the mixture of Clostridium Perfringens Type D Antitoxin diluted 1:34 and 10 L_0 doses of Standard Toxin die, the antitoxin is considered to contain less than 34 International Units per ml and the serial is unsatisfactory.

[39 FR 16859, May 10, 1974. Redesignated at 39 FR 25463, July 11, 1974, as amended at 40 FR 760, Jan. 3, 1975. Redesignated at 55 FR 35561, Aug. 31, 1990, as amended at 56 FR 66784, Dec. 26, 1991; 61 FR 51777, Oct. 4, 1996]

§§ 113.456–113.498 [Reserved]

§ 113.499 Products for treatment of failure of passive transfer.

A product for the treatment of failure of passive transfer (FPT) shall contain a specified minimum quantity of IgG per dose and shall be recommended for use only in neonates of the same species as that of antibody origin. A product for oral administration shall not be recommended for use in animals more than 24 hours of age, while one for parenteral administration shall only be recommended for use in neonatal animals. Each serial shall meet the applicable general requirements provided in §113.450 and be tested for potency as provided in this section. Any serial found unsatisfactory by a prescribed test shall not be released.

(a) *Qualification of an IgG Reference Product.* An IgG Reference Product (reference) shall be a serial of product that is manufactured according to the filed Outline of Production, properly qualified, and used to assess the potency of subsequent product serials, as described in paragraph (c) below. The reference shall be qualified as follows:

(1) At least 20 newborn, colostrum-deprived animals of the species for which the product is recommended shall be randomly selected.

(2) Blood samples shall be taken from each animal.

(3) Each animal shall be administered one dose of reference by the recommended route and shall be observed for 24 hours.

(i) Any adverse reactions shall be recorded.

(ii) The dosage of reference administered to each animal shall be in accordance with label directions. Label directions may indicate a single dosage regardless of weight, in which case the animals in the study shall be at or near the maximum weight for neonates of the species.

(4) After 24 hours, blood samples shall be taken from each animal.

(5) Pretreatment and post treatment serum IgG concentrations shall be concurrently determined for each animal using a radial immunodiffusion (RID) method acceptable to APHIS and described in the filed Outline of Production for the product.

(6) Concurrently, using the same method, five IgG measurements shall be made on an IgG Species Standard supplied or approved by APHIS. The IgG Species Standard shall be a preparation that contains IgG specific for the species in question at a concentration acceptable to APHIS.

(7) For an IgG Reference Product to be satisfactory, all animals used to qualify the reference must remain free of unfavorable product-related reactions and at least 90 percent of the paired serum samples must reflect an increase in IgG concentration (posttreatment minus pretreatment concentration) equal to or greater than the IgG concentration of the IgG Species Standard.

(b) *Antibody functionality*. Prior to licensure, the prospective licensee shall perform a neutralization study, or another type of study acceptable to APHIS, to demonstrate functionality of product antibody.

(c) *Potency*. Bulk or final container samples of completed product from each serial shall be tested for IgG content as provided in this paragraph. Samples of the test serial and of an IgG Reference Product established in accordance with paragraph (a) of this section shall be concurrently tested for IgG content by the RID method referred to in paragraph (a)(5) of this section. Five IgG measurements shall be made on each. If the IgG level per dose of the test serial does not meet or exceed that of the reference, one complete retest, involving five IgG measurements on both the reference and two samples of the test serial, may be conducted. If, upon retest, the average IgG level per dose of the two samples of the test serial does not meet or exceed that of the reference, or if a retest is not conducted, the serial is unsatisfactory.

[61 FR 51777, Oct. 4, 1996]

PART 114—PRODUCTION REQUIREMENTS FOR BIOLOGICAL PRODUCTS

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AUTHORITY: 21 U.S.C. 151–159; 7 CFR 2.22, 2.80, and 371.4.

SOURCE: 39 FR 16869, May 10, 1974, unless otherwise noted.

§ 114.1 Applicability.

Unless exempted by regulation or otherwise authorized by the Administrator, all biological products prepared, sold, bartered or exchanged, shipped or delivered for shipment in or from the United States, the District of Columbia, any Territory of the United States, or any place under the jurisdiction of the United States shall be prepared in accordance with the regulations in this part. The licensee or permittee shall